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# (54) SYSTEM AND METHOD FOR MONITORING AND CONTROLLING BLOOD GLUCOSE

SYSTEM UND VERFAHREN ZUR PRÜFUNG UND REGELUNG DER BLUTGLUKOSE

SYSTEME ET PROCEDE DE CONTROLE ET DE REGULATION DU GLUCOSE DANS LE SANG

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## Description

### FIELD OF THE INVENTION

The present invention relates to means for monitoring the level of glucose in blood and bodily tissues. Particularly, the invention relates to a system for monitoring glucose with glucose sensitive cells that produce an electrical response to glucose levels in their surrounding medium which is then used to determine the blood glucose level, to administer insulin or to take other measures to alter the blood glucose level such as diet adjustment.

### BACKGROUND OF THE INVENTION

Diabetes is a metabolic disorder that afflicts tens of millions of people in the developed countries of the world, with many millions more probably affected in underdeveloped nations. Diabetes results from the inability of the body to properly utilize and metabolize carbohydrates, particularly glucose. Normally, the finely-tuned balance between glucose in the blood and glucose in bodily tissue cells is maintained by insulin, a hormone produced by the pancreas which controls, among other things, the transfer of glucose from blood into body tissue cells. Upsetting this balance causes many complications and pathologies including heart disease, coronary and peripheral artery sclerosis, peripheral neuropathies, retinal damage, cataracts, hypertension and coma and death from hypoglycemic shock.

In patients with insulin-dependent diabetes, the symptoms of the disease can be controlled by administering additional insulin (or other agents that have similar effects) by injection or by external or implantable insulin pumps. The "correct" insulin dosage is a function of the level of glucose in the blood. Ideally, insulin administration should be continuously readjusted in response to changes in blood glucose level. However, at present, blood glucose levels can only be determined directly by a blood sample. Unfortunately, since drawing the sample is invasive, blood glucose is usually only determined once daily or less often. As a result, insulin dosage is not optimally coordinated with blood glucose levels and complications can continue to be manifested. It would, therefore, be desirable to provide non-invasive means for more closely monitoring blood glucose levels and coordinating insulin dosages with such levels.

Many attempts have been made to develop a reliable less invasive or non-invasive way to measure blood glucose level. One of the most widely used methods has been measurement of glucose excreted in the urine, which is under certain conditions an indicator of blood glucose concentration. In its most convenient form, a "dipstick," which has been coated with chemical reagents, is dipped into a urine sample. Glucose in the urine then reacts with the chemical reagents on the dipstick to produce a color change which corresponds to the appropriate range of concentration. The level of urine glucose is then correlated with blood levels on the basis of statistical data and previous experience with the specific patient. However, urine testing has presented several drawbacks. Foremost, is the tenuous link between urine glucose level and blood glucose levels. Although general trends in blood levels within a certain range are usually reflected in urine levels, moderate or periodic fluctuations of blood levels may not be reflected in urine content. Therefore, any dosage change made on the basis of urine analysis is not finely-tuned to blood levels. Furthermore, other substances in urine can cause inaccuracy in measurement by interfering with chemical reactions necessary to produce the color change on the dipstick. Finally, like blood sampling urine analysis can only be performed at relatively widely spaced intervals when the patient produces urine for analysis.

Other systems have been proposed for monitoring blood glucose levels by implanting a glucose sensitive probe into the patient. Such probes have measured various properties of blood or other tissues, including optical absorption, electrochemical potential and enzymatic products. U.S. Patent Nos. 4,436,094 and 4,704,029 disclose two examples of blood glucose level probes. U.S. Patent No. 4,436,094 utilizes an implantable electrode which contains a charged carbohydrate species which, in the absence of glucose, is bound to a component of the electrode and does not affect the potential measured by the electrode. In the presence of glucose, however, charged carbohydrate is displaced from the binding component by molecules of glucose, and as a result of its charge, affects the potential measurement by the electrode. The measured potential can then be correlated to the concentration of glucose.

U.S. Patent No. 4,704,029 discloses an implantable glucose monitor that utilizes a refractometer which measures the index of refraction of blood adjacent to an interface with the transparent surface of the refractometer by directing laser light at the interface to measure the index of refraction of the blood by the amount of radiation reflected at the interface. As the blood glucose concentration increases, the index of refraction of blood increases. By comparing the intensity of the light reflected by the blood with the intensity of light before contact in the blood, glucose concentration can be determined.

Another approach to tying blood glucose levels to insulin dosage has centered around the implantation of pancreatic cells which produce insulin in response to changes in blood glucose levels as shown for example in Altman et al., Diabetes 35:625-633 (1986): Recordi et al. ; Diabetes 35:649-653 (1986); Amsterdam et al., J. Cell Biol. 63:1037-1056 (1974); Brown et al., Diabetes 25:56-64 (1976); Carrington et al., J. Endocr. 109:193-200 (1986); and Sonerson et al., Diabetes 32:561-567 (1983). Altman et al. were able to maintain normal blood glucose levels in diabetic mice by implanting cells (1) in area impermeable to antibodies, (2) suppressing the immunogenecity of the implantable cells in tissue culture before the implantation and (3) enclosing the cells in a

capsule that was impermeable to antibodies. However, the implantation methods of Altman et al. and others are severely limited by the availability of large enough masses of cells for effective implantation and by the ability to reliably get insulin production over extended periods after implantation.

## SUMMARY OF THE INVENTION

In accordance with the present invention, systems are disclosed with implanted glucose sensitive living cells to monitor blood glucose levels by monitoring glucose levels in body tissues in which the glucose level is in equilibrium with that of the blood. In this respect, the implanted cells are similarly situated to endogenous insulin secreting glucose sensitive cells. The implanted cells produce a detectable electrical or optical signal in response to changes in glucose concentration in surrounding tissue. The signal is then detected and interpreted to give a reading indicative of blood glucose levels. This reading can then be used as a basis for altering insulin or other drug dosage for injection, as a basis for giving instructions to an external implanted insulin pump to alter the amount of insulin delivered by the pump, or as a basis for taking other corrective measures, such as altering diet. As a result, blood sugar levels can be more closely monitored and controlled in a noninvasive way and insulin dosage can be more closely tailored with concomitant control of symptoms associated with diabetes.

A system for monitoring tissue and blood glucose level is disclosed which comprises glucose sensitive cells which are capable of producing a signal in response to changes in glucose concentration in the medium surrounding the cells The signal produced can either be electrical or optical. In certain embodiments, the cells are contained in a capsule which is constructed from a membrane or similar substance which is impermeable to antibodies, yet permeable to nutrients to keep the cells alive. The capsule can also be fitted with means for collecting the signals produced by the cells.

In instances where the signal is electrical, these collecting means can be metal electrodes which are placed in contact with the cells such that the signal produced by the cells can be measured as a potential difference between the electrodes. The system can further include an implanted signal pickup device which is connected to the electrodes in the capsule for processing (e.g., amplifying and modulating) the signal for later transmission through the body surface, such as the skin, or for transmission to an external or implanted insulin pump. Once the signal is process the pickup device passes the signal on to means for transmitting the processed signal. In other embodiments, the implanted cells produce an electrical signal which can be detected by external electrodes without employing electrodes in the capsule or an implantable signal pick-up device.

In instances where the signal is optical, the signal is produced by a change in the optical qualities of the cells or specifically the membranes containing the implanted cells. Preferably the signal is produced by dyes contained within or coated on cellular membranes which will change the optical properties of the cells in response to changes in electrical activity of the cell. This change in optical quality can be detected through relatively transparent body surfaces, such as thin skin layers or fingernails. Alternatively, the optical change can be measured by an implanted optical detector which processes the detected signal much as the implanted pick-up device previously described processes electrical signals. The processed signal can be used to control an insulin pump or transmitted through the skin for external detection.

The electrical signal or the optical signal is detected through the skin by an external sensor and then correlated to a corresponding blood glucose level. The sensor includes means for detecting the signal, means for processing such signal and correlating it to the corresponding blood glucose level, and output means for reporting or relating the blood glucose level as determined.

Alternatively, the implanted signal pickup device can pass a processed signal on to an implanted insulin pump, which, in response to such signal, delivers an appropriate dosage of insulin corresponding to the determined blood glucose level.

Capsules for use in practicing the present invention are also disclosed which comprise a membrane which is impermeable to antibodies and is permeable to nutrients necessary for cell growth. Glucose sensitive cells are enclosed within the membrane, along with electrodes in contact with the cells such that changes in the electrical activity of the cells can be detected as a potential difference between the electrodes.

Alternatively, in place of the electrodes, the capsules can enclose means for "shorting-out" the interior of the capsule with respect to the exterior of the capsule such that the electrical activity of the cells is optimally dissipated on the exterior of the capsule. As a result, the electrical activity will be maintained at a level which can be detected by appropriate sensing means.

Capsules ore also disclosed which contain glucose sensitive cells which have been treated such that the cellular membranes of the cells are coated with dyes which are sensitive to change in cellular membrane potential.

Finally, methods of monitoring the blood glucose level employing the system of the present invention are disclosed. Basically, those methods comprise the use of implantable glucose-sensitive living cells, detecting the signal produced by the cells in response to levels and/or changes in glucose concentration and correlating that signal with the corresponding blood glucose level. Methods of administering glucose are also disclosed which comprise administering a level of insulin (or other correcting agent) appropriate to the blood glucose level determined in accordance with the methods disclosed herein. Such insulin can be either administered manually or by operation of an external or implanted insulin pump which is connected to the detecting and monitoring sys-

tem. It is understood that other therapeutic agents which will alter blood glucose levels, such as those sold under the tradenames "Die Beta" (glyburide; Hoechst-Roussel), "Glucontrol" (glipizide, Pfizer) and "Diabinese" (chlorpropamide; Pfizer), can be substituted for insulin as described herein.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a schematic representation of the components and operation of a system of the present invention.

Figure 2 depicts bursts of spiked electrical activity produced by pancreatic beta cells in response to various glucose concentrations.

Figure 3 contains graphs of electrical activity of six different preparations of beta cells in response to varying glucose concentration.

Figures 4 and 5 are schematic representations of the electrical components of systems of the present invention.

Figures 6A, 6B and 7 depict possible arrangements of the components of a system of the present invention with respect to the skin.

Figure 8 depicts one embodiment of a system of the present invention that utilizes an optical signal.

DETAILED DESCRIPTION OF THE INVENTION

Figure 1 schematically describes one embodiment of a system of the present invention which is described in further detail below. As shown at the upper right of Figure 1, glucose diffuses from the bloodstream into the extracellular space in bodily tissues. Eventually the glucose diffuses to implanted glucose sensitive cells which are a part of the system of the present invention. The implanted cells respond by exhibiting electrical activity, such as a change in membrane potential, commensurate with the concentration of glucose in the extracellular space.

The electrical activity can be detected or monitored in one of two ways. Where the electrical activity is strong enough to be detected through a body surface (e.g. layers of skin), the electrical activity is detected directly by an external signal sensor. Alternatively, the electrical activity is monitored by an implanted signal pickup device. The pickup device processes and amplifies the electrical activity. The amplified signal is then transmitted through a body surface (such as the skin) and is detected by the external signal sensor.

The external signal sensor contains or is connected to a decoder or microprocessor that interprets the signal. The decoder correlates the signal with blood glucose concentration on the basis of an algorithm and programmed information relating to the correlation between blood glucose levels and glucose levels at the implantation site for the patient in which the system is implanted. For example, the microprocessor can be programmed to correlate a glucose concentration of 20mM at the implantation site with a concentration of 22mM in the blood on the basis of prior and periodic blood sampling. Once the signal has been correlated and translated into a reading of the blood glucose concentration, the concentration information is used in one of two ways. First, the information can be displayed for reading by the patient or a person caring for the patient. On the basis of the displayed concentration, the correct insulin dose can be administered or diet can be adjusted. Alternatively, the concentration information is fed into an insulin pump, external or implanted that infuses the correct insulin dosage on the basis of the determined blood glucose level. The concentration information can also be fed to other devices (such as automatic liquid feeding apparatus) which will take corrective action on the basis of such information.

The systems of the present invention utilize glucose sensitive living cells as sensors of the blood sugar levels either directly (by implantation in the bloodstream) or indirectly (by implantation in tissues in equilibrium with blood glucose levels). Any cell type that produces a detectable electrical activity in response to changes in glucose concentration in the surrounding environment can be used in practicing the present invention.

Beta cells from the islets Of Langerhans in the pancreas are preferred glucose sensitive cells. Beta cells have been shown to produce electrical activity, action potentials, in response to glucose concentration and have the advantage that they respond properly to glucose in the concentration range relevant to patient monitoring, Scott et al., Diabetologia 21:470-475(1981); Pressel et al., Biophys. J. 55:540a (1989); Hidalgo et al., Biophys. J. 55:43a (1989); Atwater et al., Biophys. J. 55:7a (1980). Beta cells respond to glucose in bursts of spikes of electrical activity. The spike frequency, burst duration and pauses between bursts are all functions of glucose concentration. Figures 2 and 3 present data relating to the electrical activity of beta cells. As shown in Figure 2, the burst duration increases as glucose concentration increases. The pause between bursts also decreases as glucose concentration increases. In Figure 3, the spike frequency (spikes/second) increases as glucose concentration increases. Each of these parameters (burst duration, pause duration and spiek frequencexx), as well as spike shape, can be monitored alone or in combination as a source of signal corresponding to cellular electrical activity. It has also been established that the beta cells are electrically coupled, resulting in synchronized electrical activity of the cells. Eddlestone et al., J. Membrane Biol. 77:1-141 (1984), Meda et al., Quarterly J. Exper. Physio. 69:719-735 (1984). Therefore, in response to a change in the glucose concentration many cells fire their action potentials or electric signals in synchrony, producing a significantly amplified signal which is easier to detect.

Methods of isolating beta cells are described in the references cited in th preceding paragraph and in Amsterdam et al., J. Cell Biol. 63:1037-1056 (1979); Ricordi et al., Diabetes 35:649-653 (1986); and Car-

rington et al., Endocr. 109:193-200 (1986). In addition, any other method for isolating beta cells can be used which preserves the ability of the isolated cells to respond to changes in glucose concentration. Other methods for culturing pancreatic cells are disclosed in Amsterdam et al., J. Cell Biol. 63: 1037-1073 (1974); Amsterdam et al., Proc. Natl. Acad. Sci. USA 69:3028-3032 (1972), Ciba Foundation Symposium on the Exocrine Pancreas, Reuck and Cameron, ed., p. 23-49 (J. and A. Churchill Ltd., London 1962); and Howard et al., J. Cell Biol. 35: 675-684 (1967).

Sensory cells in taste buds have also been shown to respond to fluctuations in glucose concentrations. Ozeki, J. Gen. Physiol. 58:688-699 (1971); Avenet et al., J. Membrane Biol. 97:223-240 (1987); Tonosaki et al.; Brain Research 445:363-366 (1988). Taste cells show particular advantage for systems of the present invention because under suitable conditions such cells regenerate every few days by continuous division. Thus, prolonged growth of these cells when implanted is more readily sustained. Taste cells can be removed from a patient with only minor surgery, grown in culture to obtain a sufficient number of cells and then implanted. The ability to use a patient's own cells also reduced the likelihood of immunologic reactions to the implant. Taste cells can be isolated according to the methods of the publications cited above or by any other method which preserves the ability of the cells to respond to change in glucose concentration.

Alpha cells from the pancreas have also been shown to be sensitive to glucose concentrations in the surrounding medium. Sonerson et al., Diabetes 32:561-567 (1983). Transformed cell lines, such as the insulin producing line disclosed in U.S. Patent No. 4,332,893, and hybridoma lines can also be used. Any electrical activity associated with the response by alpha cells or transformed lines to glucose can be harnessed in practicing the present invention.

Many methods are known for implanting beta cells in human tissues. Altman et al., Diabetes 35:625-633 (1986); Ricordi et al., Diabetes 35:649-653 (1986); Brown et al., Diabetes 25:56-64 (1976); Schmidt et al., Diabetes 32:532-540 (1983). Other means for encapsulating living cells are disclosed in U.S. Patent Nos. 4,663,286, 4,409,331, 4,352,883, 4,798,786, 4,689,293 and 4,353,888. Although the implanted cells of the present invention need not necessarily be encapsulated, any of these methods can be employed to produce an implantable capsule where such is used. The method of Altman et al. is preferred. The Altman capsule is a thin walled (about 100 microns thick) tube or elongated pellet made of a polyvinyl chloride acrylic copolymer, with a diameter of about 1 mm. These dimensions are preferred to maintain proper diffusion to all cells. The molecular-weight cut off of the Altman et al. capsule membrane was approximately 50,000. In preferred embodiments of the present invention, the cut off is less than 50,000 and most preferably between 1,000 and 10,000.

The capsule serves two basic functions. First, it serves as a barrier that prevents the cells from migrating away, while nutrients and waste products are free to diffuse through the capsule. Second, it serves to prevent antibodies and other large molecules from leaving or entering the capsule, for example, to prevent immunological reactions. The capsule also allows the use of glucose sensitive tumor cell lines as sensor cells which must be contained to prevent proliferation. Any material which will provide these functions can be used to form capsules containing glucose sensitive cells.

In some embodiments, while not significantly interfering with production and detection of cellular electrical activity, the capsules are equipped with means for aiding detection of cellular electrical activity, such as electrodes or conducting bars that short-circuit the cell electric activity with the outside. The capsules are also preferably implanted in clusters so as to ensure a detectable signal even if one or more capsules becomes disfunctional. The capsules may also contain means to fix them in the desired location or materials useful for determining the location of the capsules, such as radio-opaque materials.

Where the electrical activity is too low to be detected through th body surface without amplification or where the electrical activity is to be harnessed to drive an insulin pump, electrodes are placed on the inside of the capsule such that a potential difference can be measured across the electrodes which corresponds to the electrical activity of the cells inside the capsule. To prevent cell damage, these should be made from an inert metal, such as those commonly used in a variety of implants. See for example, "Cardiac Pacing and Physiology," Proceedings of the VIIIth World Symposium on Cardiac Pacing and Electrophysiology, Jerusalem, Israel, June 2-11, 1987, ed. Belhassen et al., (Keterpress Enterprises, Jerusalem); IEE Trans. Biomed. Eng. 34:664-668 (1987); and J. Am. Coll. Cardiol. 11:365-370 (1988). Since these electrodes are used for signal pickup only and not for electric stimulation, their functional lifetime should be practically indefinite. The electrodes are connected by insulated wires to an implanted signal pickup device for processing and amplification or to the insulin pump.

First, where the electrical activity of the implanted cells generates electrical signals strong enough to be picked up from the external body surface by electrodes (as in EEG or ECG), the capsules are implanted near the surface of the skin where the skin is very thin and the location convenient. As shown in Fig. 6B, the signal is then detected by the external signal sensor. Alternatively, where the electrical activity is too small to be picked up by external means, electrodes are introduced into the capsule and connected to the implanted signal pickup device as shown in Figure 6A. In this case the capsule implantation can be done anywhere in the body, for example, the peritoneal cavity where implantation is relatively easy and vascularization is adequate.

The basis components of the implanted signal pickup device are shown in Fig. 5. Basically, the device

resembles implanted pacemakers in its external surface property. It can contain some or all of the following elements as necessary to provide a processed signal which is suitable for transmission or other desired use:

1. Inputs connected to the electrodes inside the implanted capsules.
2. A number of low noise, high input impedence differential preamplifiers corresponding to the number of capsules. Preferably, each capsule is connected to a single differential input amplifier.
3. Band pass filters at the outputs of the amplifiers. In certain embodiments, each amplifier may be connected through two filters, one designed to pass only the spikes (action potentials) while the other will pass only the very slow potential shifts associated with each burst of activity.
4. An integrating amplifier or microprocessor that sums up the output of all the preamplifiers.
5. A coding and modulating microprocessor that processes the summed signal so as to be best suitable for transmission across the skin, such as FM modulation.
6. A power amplifier that boosts the processed signal and is connected to the transmitter that sends the processed signal through the skin.

There are two preferred alternative modes of transmission of the data from the internal implanted amplifier across the skin to the external sensor. In the first alternative, the amplifier is driven by low amplitude local currents by means of a pair of electrodes implanted under the skin. The electric field thus created is similar to those generated by the heart (such as in ECG measurement) and can be detected similarly by external electrodes. AC modulation of these currents will prevent local tissue stimulation, electrode polarization, and the like. In the second alternative, the output of the amplifier is fed, after proper modulation, to an induction coil or a coupling capacitive signal transferer. This coil generates an eletromagnetic field that is picked up by a similar externally positioned coil. Other means for transmitting a signal across the tissue barrier will be apparent to skilled artisans and may be used in practicing the present invention.

The signal from the capsules or the transmitter of the signal pickup device is detected by an external signal sensor. The basic components of the signal sensor are shown in Figs. 4 and 6. In certain embodiments, the signal sensor can include one or more of the following elements:

1. A sensor, such as an electrode coil or other means suited to detect the electrical or optical signal transmitted through the body surface.
2. A preamplifier connected to the sensors (which may not be necessary where the signal is already amplified before transmission across the skin barrier).
3. A filter for external noise reduction.
4. A demodulator - decoding microprocessor that separates the signals from their FM carrier or other modulation means when such a mode of transmission is used.
5. A signal processor that utilizes the appropriate algorithms and programmed information relating to glucose concentration to translate the transmitted signal into the corresponding glucose concentration.

The processed and decoded signal corresponding to determined glucose concentration is then passed on to means for outputting such information in the desired manner. For example, the concentration information can be presented as a digital readout in the form of a digital display on the probe itself or a display and printout in an associated device. A memory may be used to save the glucose values obtained during continuous or frequent glucose level monitoring. Such information including integretated glucose levels may also be used for determination of the correct amounts of insulin or insulin like drugs to be taken by the patient or determining patient diet. Such information can be displayed for patient use or as an input to an automated insulin infusion device.

A calibration system can also be associated with the system of the present invention. Since the exact dependency of electrical activity of the implanted cells on glucose concentration may vary with time, a means for recalibration of the system is provided. Upon calibration the external device or probe is put into calibration mode. The current blood glucose level, as determined by a blood sample or other reliable means is fed manually (or automatically) to the calibration circuit that will reset the proper parameters of the concentration determining algorithms. A second glucose determination may be necessary at times to obtain two points on the calibration curve. Calibrations can be performed as frequently or infrequently as necessary to achieve and maintain the desired degree of accuracy in glucose level determination.

As shown in Fig. 7, in certain embodiments the processed signal is used to control an implanted insulin pump. By means of the controller the pump output is kept relatively consistent with the blood glucose levels thus allowing the pump to more closely mimic the human pancreas. Most commercially available implantable pumps can be adapted for such use giving the pump similar properties to those of the beta cells.

An alternate embodiment of a system of the present invention converts the electrical activity of the glucose sensitive cells into an optical signal. Direct changes in cell optical properties resulting from electrical activity can be measured as an optical signal. Alternatively, biocompatible dyes which are sensitive to electric fields can be incorporated into the cell membranes and subjected to the membrane potential or electric field. Dyes useful for practicing this embodiment are disclosed in Grinvald et al., Physiol. Rev. 68:1285-1366 (1988) and Gross et al., Biophys. J. 50:339-348 (1986). Other suitable dyes

include those commercially available from Molecular Probes, Inc., Eugene, Oregon. The changes in the membrane potential induce changes in the optical properties of untreated cells or dyed cells, for example, in the optic density, fluorescence or birefringence of the cell membrane. Thus, the action potential or electric spikes that the cells generate in response to glucose concentration induce changes in the optical properties of the cells (i.e., they generate optical signals). These signals are picked up by an implanted or external optical sensor In certain embodiments, the cells are implanted such that a transparent body surface, such as thin skin layers or fingernails separates them from the outside world. In optical signal embodiments, if a capsule is used, it must be constructed from a material through which the optical changes can be stimulated and measured (e.g., practically all thin plastics). One such implanatation of cells is shown in Fig. 8. As shown an external optical sensor monitors the cell activity and translates it into glucose concentration data. The external sensor can include a light source of the proper wavelength to excite the dyes or to be reflected from the cell surfaces and other components previously described for the eternal electrical signal sensor for processing, decoding and outputting the signal. Alternatively, the optical sensing components can be implanted such that an electrical signal, corresponding to the optical signal, is produced which can be detected or transmitted through the skin.

## Claims

1. A system for monitoring glucose levels in a patient's body tissues, said system comprising:

   implantable glucose-sensitive living cells capable of producing an electrical or optical signal in response to the glucose concentration in the medium surrounding said cells in the patient; and means located externally to the living cells for non-invasively detecting said electrical or optical signal.

2. The system of Claim 1 wherein said signal is an electrical signal.

3. The system of Claim 2 wherein said cells are contained in a capsule and wherein the means for detecting said electrical or optical signal comprises collecting means in said capsule for collecting said electrical signal from said cells.

4. The system of Claim 3 wherein said collecting means are metal electrodes in contact with said cells such that said signal can be measured as a potential difference between said electrodes.

5. The system of Claim 4 wherein the means for detecting said electrical signal further comprises an implantable signal pickup device connected to said electrodes for processing said signal for transmission.

6. The system of Claim 5 wherein the means for detecting said electrical signal further comprises transmission means connected to said pickup device for transmitting said processed signal through a body surface.

7. The system of Claim 1 wherein said signal is optical.

8. The system of Claim 7 wherein said signal results from changes in the optical qualities of said cells.

9. The system of Claim 8 wherein said optical qualities are changed by dyes in or on the membranes of said cells that are affected by changes in the membrane potential of said membranes.

10. The system of Claim 8 wherein the means for detecting said optical signal comprises an implantable optical sensing device positioned with respect to said cells so as to detect and process said signal for transmission.

11. The system of Claim 10 wherein the means for detecting said optical signal further comprises transmission means connected to said implantable optical sensing device for transmitting said processed signal through a body surface.

12. The system of Claims 6 or 11 wherein the means for detecting said electrical or optical signal comprises sensor means for detecting said transmitted signal through said body surface and for correlating said transmitted signal to said glucose concentration.

13. The system of Claim 12 wherein said sensor means comprises:

   detector means for detecting said transmitted signal; processor means connected to said detector means for correlating said transmitted signal to said glucose concentration; and

   output means connected to said processor means for reporting said glucose concentration.

14. The system of Claim 5 further comprising an insulin pump connected to said pickup device such that said pump delivers a dosage of insulin appropriate to said glucose concentration.

15. The system of Claim 10 further comprising an insulin pump connected to the implantable optical sensing device of the means for detecting said optical or electrical signal such that said pump delivers a dosage of insulin appropriate to said glucose concentration.

16. The system of Claim 1 wherein said cells are selected from the group comprising beta cells, alpha cells and taste cells.

17. The system of Claim 16 wherein said cells are beta cells.

18. A method of monitoring the glucose level in a patients body tissues, said method comprising:
the use of implantable glucose-sensitive living cells capable of producing an electrical or optical signal in response to glucose concentration in the medium surrounding said cells in the patient;
detecting said signal by means located externally to the living cells for non-invasive detection of said signal; and
correlating said signal with said glucose concentration.

19. The method of Claim 18 wherein said signal is detected through a body surface by an external signal sensor.

20. The method of Claim 19 wherein said signal is processed by said sensor and correlated with said corresponding glucose concentration.

21. The method of Claim 18 wherein the electrical or optical signal is detected by an implantable signal pickup device that processes said signal for transmission through a body surface.

22. The method of Claim 21 wherein said processed signal is transmitted through said body surface and is sensed externally thereof.

23. The method of Claim 22 wherein said transmitted signal is correlated with said corresponding glucose concentration.

24. The method of claim 18, wherein said method further comprises the step of administering a dosage of insulin at a level appropriate to said glucose concentration.

25. The method of Claim 24 wherein said dosage is administered by an implantable insulin pump.

26. The system of claim 1, wherein said system comprises a capsule implantable in a patient's body, said capsule comprising a thin walled tube or a pellet and being constituted of:

(a) glucose-sensitive living cells capable of producing an electrical signal in response to the glucose concentration in the medium surrounding the capsule in the patient;
(b) a membrane enclosing the cells, the membrane being impermeable to the cells and any antibodies and large molecules to prevent immunological reactions, and being permeable to nutrients for and waste products from the cells to maintain viability of the cells; and
(c) electrodes within the membrane and located externally to the living cells for non-invasively measuring the potential difference corresponding to the electrical activity of the cells;

the dimensions of the capsule being sufficient to permit implantation in the patient's body and diffusion between the cells and the medium surrounding the capsule in the body.

27. The system as defined in Claim 26 wherein the capsule comprises a thin walled tube.

28. The system as defined in Claim 26 wherein the capsule comprises a pellet made of polyvinyl chloride acrylic copolymer.

29. The system as defined in Claim 26 wherein the glucose-sensitive living cells are selected from the group consisting of beta cells, sensory cells, alpha cells, and combinations thereof.

30. The system as defined in Claim 26 wherein the electrodes comprise an inert metal.

31. The system as defined in Claim 26 wherein the membrane has a molecular weight cut-off not greater than about 50,000.

32. The system of claim 1, wherein said system comprises an implantable in a patient's body, said capsule comprising a thin walled tube or a pellet and being constituted of:

(a) glucose-sensitive living cells capable of producing an electrical signal in response to the glucose concentration in the medium surrounding the capsule in the patient;
(b) a membrane enclosing the cells, the membrane being impermeable to the cells and any antibodies and large molecules to prevent immunological reactions, and being permeable to nutrients for and waste products from the cells to maintain viability of the cells; and
(c) means for shorting out the interior of the capsule with respect to the exterior of the capsule such that electrical activity of the cells is dissipated in the exterior;

the dimensions of the capsule being sufficient to permit implantation in the patient's body and diffusion between the cells and the medium surrounding the capsule in the body.

33. The system as defined in Claim 32 wherein the capsule comprises a pellet made of polyvinyl chloride acrylic copolymer.

34. The system as defined in claim 32, wherein the capsule comprises a thin walled tube.

35. The system as defined in Claim 32 wherein the glucose-sensitive living cells are selected from the group consisting of beta cells, sensory cells, alpha cells, and combinations thereof.

36. The system as defined in Claim 32 wherein the membrane has a molecular weight cut-off not greater than about 50,000.

37. The system of claim 1, wherein said system comprises a capsule implantable in a patient's body, said capsule comprising a thin walled tube or a pellet and being constituted of:

(a) glucose-sensitive living cells capable of producing an electrical signal in response to the glucose concentration in the medium surrounding the capsule in the patient;
(b) a cellular membrane surrounding each cell, said cellular membrane containing or being coated with at least one dye whose optical properties are changed by the electrical signal produced by said cells, and
(c) the second membrane being impermeable to the cells and any antibodies and large molecules to prevent immunological reactions, and being permeable to nutrients for and waste products from the cells to maintain viability of the cells; the dimensions of the capsule being sufficient to permit implantation in the patient's body and diffusion between the cells and the medium surrounding the capsule in the body.

38. The system as defined in Claim 37 wherein the capsule comprises a thin walled tube.

39. The system as defined in Claim 37 wherein the capsule comprises a pellet made of polyvinyl chloride acrylic copolymer.

40. The system as defined in Claim 37 wherein the glucose-sensitive living cells are selected from the group consisting of beta cells, sensory cells, alpha cells, and combinations thereof.

41. The system as defined in Claim 37 wherein the membrane has a molecular weight cut-off not greater than about 50,000.--

**Patentansprüche**

1. Ein System zur Überwachung des Glukosespiegels im Körpergewebe eines Patienten, wobei das System implantierbare, glukoze-empfindliche, lebende Zellen, die imstande sind ein elektrisches oder optisches Signal zu produzieren in Antwort auf die Glukozekonzentration in dem Medium, das die Zellen im Patienten umgibt und ein außerhalb der lebenden Zellen gelegenes Mittel zum nicht eindringenden Detektieren des elektrischen oder optischen Signals enthält.

2. Das System gemäß Anspruch 1, wobei das Signal ein elektrisches Signal ist.

3. Das System gemäß Anspruch 2, wobei die Zellen in einer Kapsel enthalten sind und wobei das Mittel für das Detektieren des elektrischen oder optischen Signals ein Auffangmittel in der Kapsel für das Auffangen des elektrischen Signals aus den Zellen enthält.

4. Das System gemäß Anspruch 3, wobei das Auffangmittel mit den Zellen in Verbindung stehenden Metalelektroden ist, derart, daß das Signal als einen Potentialdifferenz zwischen den Elektroden gemessen werden kann.

5. Das System gemäß Anspruch 4, wobei das Mittel für das Detektieren des elektrischen Signals ferner eine implantierbare Signalempfangsvorrichtung enthält, die für das Verarbeiten des Signals zur Übertragung mit den Elektroden verbunden ist.

6. Das System gemäß Anspruch 5, wobei das Mittel für das Detektieren des elektrischen Signals ferner ein Übertragungsmittel enthält, das mit der Empfangsvorrichtung verbunden ist zur Übertragung des verarbeiteten Signals durch eine Körperoberfläche.

7. Das System gemäß Anspruch 1, wobei das Signal optisch ist.

8. Das System gemäß Anspruch 7, wobei das Signal aus Veränderungen in den optischen Eigenschaften der Zellen resultiert.

9. Das System gemäß Anspruch 8, wobei die optischen Eigenschaften durch Farbstoffe in oder auf den Membranen der Zellen, die durch die Veränderungen in dem Membranpotential der Membrane beeinflußt werden, verändert werden.

10. Das System gemäß Anspruch 8, wobei das Mittel für das Detektieren des optischen Signals eine implantierbare optische Sensorvorrichtung enthält, die um das Signal für Übertragung zu detektieren und zu verarbeiten im Verhältnis zu den Zellen aufgestellt ist.

11. Das System gemäß Anspruch 10, wobei das Mittel für das Detektieren des optischen Signals ferner ein Übertragungsmittel enthält, das mit der implantierbaren, optischen Sensorvorrichtung zur Übertra-

gung des verarbeiteten Signals durch eine Körperoberfläche verbunden ist.

12. Das System gemäß Anspruch 6 oder 11, wobei das Mittel für das Detektieren des elektrischen oder optischen Signals Sensormittel für das Detektieren des übertragenen Signals durch die Körperoberfläche und für das Korrelieren des übertragenen Signals mit der Glukozekonzentration enthält.

13. Das System gemäß Anspruch 12, wobei das Sensormittel enthält ein Detektormittel für das Detektieren des übertragenen Signals; ein Prozessormittel, das mit dem Sensormittel verbunden ist zum Korrelieren des übertragenen Signals mit der Glukozekonzentration; und ein Ausführmittel, das mit dem Prozessormittel verbunden ist zum Berichten der Glukozekonzentration enthält.

14. Das System gemäß Anspruch 5, das weiter eine Insulinpumpe enthält, die mit der Empfangsvorrichtung in der Weise verbunden ist, daß die Pumpe eine Dosis Insulin entsprechend der Glukozekonzentration abgibt.

15. Das System gemäß Anspruch 10, das weiter eine Insulinpumpe enthält, die mit der implantierbaren, optischen Sensorvorrichtung des Mittels für das Detektieren des optischen oder elektrischen Signals in der Weise verbunden ist, daß die Pumpe eine Dosis Insulin entsprechend der Glukozekonzentration abgibt.

16. Das System gemäß Anspruch 1, wobei die Zellen aus der Gruppe die Beta-, Alpha- und Geschmackszellen enthält, gewählt werden.

17. Das System gemäß Anspruch 16, wobei die Zellen Betazellen sind.

18. Ein Verfahren um den Glukozespiegel in dem Körpergewebe eines Patienten zu überwachen, wobei dieses Verfahren den Gebrauch von implantierbaren, glukoze-empfindlichen, lebenden Zellen, die imstande sind ein elektrisches oder optisches Signal zu produzieren in Antwort auf die Glukozekonzentration in dem Medium, das die Zellen im Patienten umgibt, das Detektieren des Signals durch ein Mittel, das außerhalb der lebenden Zellen gelegen ist, für die nicht eindringende Detektieren des Signals; und das Korrelieren des Signals mit der Glukozekonzentration,
enthält.

19. Das Verfahren gemäß Anspruch 18, wobei das Signal durch eine Körperoberfläche mittels eines externen Signal-sensors detektiert wird.

20. Das Verfahren gemäß Anspruch 19, wobei das Signal durch den Sensor verarbeitet wird und mit der entsprechenden Glukozekonzentration korreliert wird.

21. Das Verfahren gemäß Anspruch 18, wobei das elektrische oder optische Signal durch eine Signalempfangsvorrichtung detektiert wird, die das Signal zur Übertragung durch eine Körperoberfläche verarbeitet.

22. Das Verfahren gemäß Anspruch 21, wobei das verarbeitete Signal durch die Körperoberfläche übertragen wird und außerhalb dessen erfaßt wird.

23. Das Verfahren gemaß Anspruch 22, wobei das übertragene Signal mit der entsprechenden Glukozekonzentration korreliert wird.

24. Das Verfahren gemäß Anspruch 18, wobei dieses Verfahren ferner den Schritt der Verabreichung einer Dosis Insulin enthält, bei einem Spiegel der der Glukozekonzentration entspricht.

25. Das Verfahren gemäß Anspruch 24, wobei die Dosis durch eine implantierbare Insulinpumpe verabreicht wird.

26. Das System gemäß Anspruch 1, wobei das System eine Kapsel enthält, die in einem Patientenkörper implantierbar ist, wobei die Kapsel ein dünwandiges Rohr oder eine Tablette umfaßt und gebildet wird aus:

(a) glukoze-empfindlichen, lebenden Zellen, die imstande sind ein elektrisches oder optisches Signal zu produzieren in Antwort auf die Glukozekonzentration in dem Medium, das die Zellen im Patienten umgibt;

(b) einer den Zellen umgebenden Membran, wobei die Membran, um immunologische Reaktionen zu verhindern, für die Zellen und für etwaige Antikörper und für große Moleküle impermeabel ist, und für Nährmittel und Abfallprodukte aus den Zellen permeabel ist, um die Lebensfähigkeit der Zellen aufrechtzuerhalten; und

(c) Elektroden innerhalb der Membran und außerhalb der lebenden Zellen gelegen, um die Potentialdifferenz gemäß der elektrischen Aktivität der Zellen nicht-eindringend zu messen;

wobei die Abmessungen der Kapsel ausreichen um das Implantieren im Patientenkörper und die Diffusion zwischen den Zellen und dem Medium, welches die Kapsel im Körper umgibt, zu ermöglichen.

27. Das System gemäß Anspruch 26, wobei die Kapsel ein dünwandiges Rohr enthält.

28. Das System gemäß Anspruch 26, wobei die Kapsel eine aus Polyvinylchloridacrylatcopolymer bestehende Tablette enthält.

29. Das System gemäß Anspruch 26, wobei die glukoze-empfindlichen, lebenden Zellen aus der Gruppe bestehend aus Betazellen, sensorischen Zellen, Alphazellen, und Zusammensetzungen davon, ausgewählt werden.

30. Das System gemäß Anspruch 26, wobei die Elektroden ein inertes Metall enthalten.

31. Das System gemäß Anspruch 26, wobei die Membran eine molekülare Gewichtsabsperrung hat, die nicht größer ist als etwa 50.000.

32. Das System gemäß Anspruch 1, wobei das System eine Kapsel enthält, die in einem Patientenkörper implantierbar ist, wobei die Kapsel ein dünwandiges Rohr oder eine Tablette umfaßt und gebildet ist aus:

(a) glukoze-empfindlichen, lebenden Zellen, die imstande sind ein elektrisches Signal in Antwort auf die Glukozekonzentration in dem Medium, das die Kapsel im Patienten umgibt, zu produzieren;

(b) einer den Zellen umgebenden Membran, wobei die Membran für die Zellen und für etwaige Antikörper und für große Moleküle impermeabel ist, um immunologische Reaktionen zu verhindern, und für Nährmittel und Abfallprodukte aus den Zellen permeabel ist, um die Lebensfähigkeit der Zellen aufrechtzuerhalten; und

(c) Elektroden innerhalb der Membran und außerhalb der lebenden Zellen gelegen, um die Potentialdifferenz gemäß der elektrischen Aktivität der Zellen nicht-eindringend zu messen;

wobei die Abmessungen der Kapsel ausreichen um das Implantieren im Patientenkörper und die Diffusion zwischen den Zellen und dem Medium, welches die Kapsel im Körper umgibt, zu ermöglichen.

33. Das System gemäß Anspruch 32, wobei die Kapsel eine aus Polyvinylchloridacrylatcopolymer bestehende Tablette enthält.

34. Das System gemäß Anspruch 32, wobei die Kapsel ein dünwandiges Rohr enthält.

35. Das System gemäß Anspruch 32, wobei die glukoze-empfindlichen, lebenden Zellen aus der Gruppe bestehend aus Betazellen, sensorischen Zellen, Alphazellen, und Zusammensetzungen davon, ausgewählt werden.

36. Das System gemäß Anspruch 32, wobei die Membran eine molekülare Gewichtsabsperrung hat, die nicht größer ist als etwa 50.000.

37. Das System gemäß Anspruch 1, wobei das System eine Kapsel enthält, die in einem Patientenkörper implantierbar ist, wobei die Kapsel ein dünwandiges Röhrchen oder eine Tablette umfaßt und gebildet wird aus:

(a) glukoze-empfindlichen, lebenden Zellen, die imstande sind ein elektrisches Signal in Antwort auf die Glukozekonzentration in dem Medium, das die Kapsel im Patienten umgibt, zu produzieren;

(b) einer zelligen Membran, die jede Zelle umgibt, wobei die zellige Membran zumindest einen Farbstoff enthält oder damit beschichtet ist, wessen optische Eigenschaften durch das elektrische Signal, das durch die Zellen produziert wird, verändert werden, und

(c) wobei die zweite Membran für die Zellen und für etwaige Antikörper und für große Moleküle impermeabel ist, um immunologische Reaktionen zu verhindern, und für Nährmittel und Abfallprodukte aus den Zellen permeabel ist, um die Lebensfähigkeit der Zellen aufrechtzuerhalten; wobei die Abmessungen der Kapsel ausreichen um das Implantieren im Patientenkörper und die Diffusion zwischen den Zellen und dem Medium, welches die Kapsel im Körper umgibt, zu ermöglichen.

38. Das System gemäß Anspruch 37, wobei die Kapsel ein dünwandiges Rohr enthält.

39. Das System gemäß Anspruch 37, wobei die Kapsel eine aus Polyvinylchloridacrylatcopolymer bestehende Tablette enthält.

40. Das System gemäß Anspruch 37, wobei die glukoze-empfindlichen, lebenden Zellen aus der Gruppe bestehend aus Betazellen, sensorischen Zellen, Alphazellen, und Zusammensetzungen davon, ausgewählt werden.

41. Das System gemäß Anspruch 37, wobei die Membran eine molekülare Gewichtsabsperrung hat, die nicht größer ist als etwa 50.000.

## Revendications

1. Système de surveillance des niveaux de glucose dans les tissus du corps d'un patient, ledit système comprenant :
   des cellules vivantes implantables sensibles au glucose, capables de produire un signal électrique ou optique en réponse à la concentration en glucose dans le milieu environnant lesdites cellules dans le patient ; et un moyen placé à l'extérieur des cellules vivantes pour la détection sans intrusion dudit signal électrique ou optique.

2. Système selon la revendication 1, dans lequel ledit signal est un signal électrique.

3. Système de la revendication 2, dans lequel lesdites cellules sont contenues dans une capsule, et dans lequel le moyen de détection dudit signal électrique ou optique comprend des moyens de collecte dans ladite capsule pour la collecte dudit signal électrique émanant desdites cellules.

4. Système selon la revendication 3, dans lequel lesdits moyens de collecte sont des électrodes métalliques en contact avec lesdites cellules, de telle sorte que ledit signal peut être mesuré sous la forme d'une différence de potentiel entre lesdites électrodes.

5. Système selon la revendication 4, dans lequel le moyen de détection dudit signal électrique comprend en outre un dispositif capteur de signaux implantable, connecté auxdites électrodes pour le traitement dudit signal pour sa transmission.

6. Système selon la revendication 5, dans lequel le moyen de détection dudit signal électrique comprend en outre un moyen de transmission connecté audit dispositif capteur, pour transmettre ledit signal traité au travers de la surface d'un corps.

7. Système selon la revendication 1, dans lequel ledit signal est optique.

8. Système selon la revendication 7, dans lequel ledit signal est le résultat de modifications dans les caractéristiques optiques desdites cellules.

9. Système selon la revendication 8, dans lequel lesdites caractéristiques optiques sont modifiées par des colorants dans ou sur les membranes desdites cellules, qui sont affectées par les modifications du potentiel de membrane desdites membranes.

10. Système selon la revendication 8, dans lequel le moyen de détection dudit signal optique comprend un dispositif de lecture optique implantable positionné par rapport auxdites cellules de façon à détecter et à traiter ledit signal pour sa transmission.

11. Système selon la revendication 10, dans lequel le moyen de détection dudit signal optique comprend en outre un moyen de transmission connecté audit dispositif de lecture optique implantable, pour transmettre ledit signal traité au travers de la surface d'un corps.

12. Système selon les revendications 6 ou 11, dans lequel le moyen de détection dudit signal électrique ou optique comprend un moyen de lecture pour détecter ledit signal transmis au travers de ladite surface d'un corps, et pour mettre ledit signal transmis en corrélation avec ladite concentration en glucose.

13. Système selon la revendication 12, dans lequel ledit moyen de lecture comprend :
   un moyen de détection pour détecter ledit signal transmis
   un moyen de traitement de l'information connecté audit moyen de détection pour mettre ledit signal transmis en corrélation avec ladite concentration en glucose ; et
   un moyen de sortie connecté audit moyen de traitement de l'information pour rendre compte de ladite concentration en glucose.

14. Système selon la revendication 5, comprenant en outre une pompe à insuline connectée audit dispositif capteur de telle sorte que ladite pompe fournit une dose d'insuline appropriée à ladite concentration en glucose.

15. Système selon la revendication 10 comprenant en outre une pompe à insuline connectée au dispositif de lecture optique implantable du moyen de détection dudit signal optique ou électrique, de telle sorte que ladite pompe fournit une dose d'insuline appropriée à ladite concentration en glucose.

16. Système de la revendication 1, dans lequel lesdites cellules sont sélectionnées à partir d'un groupe comprenant des cellules bêta, des cellules alpha, et des cellules sensorielles.

17. Système selon la revendication 16, dans lequel lesdites cellules sont des cellules bêta.

18. Procédé pour le contrôle du niveau de glucose dans les tissus du corps d'un patient, ledit procédé comprenant :
   l'utilisation de cellules vivantes implantables sensibles au glucose, capables de produire un signal électrique ou optique en réponse à la concentration en glucose dans le milieu environnant lesdites cellules dans le patient ;
   la détection dudit signal par un moyen placé

à l'extérieur des cellules vivantes pour la détection, sans intrusion, dudit signal ; et

la mise dudit signal en corrélation avec ladite concentration en glucose.

19. Procédé selon la revendication 18, dans lequel ledit signal est détecté au travers de la surface d'un corps par un lecteur de signaux externe.

20. Procédé selon la revendication 19, dans lequel ledit signal est traité par ledit lecteur et mis en corrélation avec ladite concentration en glucose correspondante.

21. Procédé selon la revendication 18, dans lequel le signal électrique ou optique est détecté par un dispositif capteur de signaux implantable, qui traite ledit signal pour sa transmission à travers la surface d'un corps.

22. Procédé selon la revendication 21, dans lequel ledit signal traité est transmis à travers ladite surface d'un corps, et est lu à l'extérieur.

23. Procédé selon la revendication 22, dans lequel ledit signal transmis est mis en corrélation avec ladite concentration en glucose correspondante.

24. Procédé selon la revendication 18, dans lequel ladite procédé comprend en outre l'étape qui consiste à administrer une dose d'insuline à un niveau approprié à ladite concentration en glucose.

25. Procédé selon la revendication 24, dans lequel ladite dose est administrée par une pompe à insuline implantable.

26. Système selon la revendication 1, dans lequel ledit système comprend une capsule implantable dans le corps d'un patient, ladite capsule comprenant un tube à paroi mince ou une pastille et étant constituée de :

(a) cellules vivantes sensibles au glucose, capables de produire un signal électrique en réponse à la concentration de glucose dans le milieu environnant la capsule dans le patient ;
(b) une membrane enfermant les cellules, la membrane étant imperméable aux cellules et à tous anticorps et grosses molécules pour empêcher des réactions immunologiques, et étant perméable aux substances nutritives des cellules, et aux déchets émanant des cellules, pour maintenir la viabilité des cellules ; et
(c) des électrodes à l'intérieur de la membrane et placées à l'extérieur des cellules vivantes pour mesurer sans intrusion la différence de potentiel correspondant à l'activité électrique des cellules ; les dimensions de la capsule étant suffisantes pour permettre l'implantation dans le corps du patient et la diffusion entre les cellules et le milieu environnant la capsule dans le corps.

27. Système selon la revendication 26, dans lequel la capsule comprend un tube à paroi mince.

28. Système selon la revendication 26, dans lequel la capsule comprend une pastille faite d'un copolymère acrylique de polyvinylchlorure.

29. Système selon la revendication 26, dans lequel les cellules vivantes sensibles au glucose sont sélectionnées à partir du groupe composé de cellules bêta, cellules sensorielles, cellules alpha, et de combinaisons entre elles.

30. Système selon la revendication 26, dans lequel les électrodes comprennent un métal inerte.

31. Système selon la revendication 26, dans lequel la membrane présente une masse moléculaire critique ne dépassant pas environ 50 000.

32. Système selon la revendication 1, dans lequel ledit système comprend une capsule implantable dans le corps d'un patient, ladite capsule comprenant un tube à paroi mince ou une pastille et étant constituée de :

(a) cellules vivantes sensibles au glucose, capables de produire un signal électrique en réponse à la concentration de glucose dans le milieu environnant la capsule dans le patient ;
(b) une membrane enfermant les cellules, la membrane étant imperméable aux cellules et à tous anticorps et grosses molécules pour empêcher des réactions immunologiques, et étant perméable aux substances nutritives des cellules, et aux déchets émanant des cellules, pour maintenir la viabilité des cellules ; et
(c) un moyen pour mettre l'intérieur de la capsule en court-circuit par rapport à l'extérieur de la capsule, de telle sorte que l'activité électrique des cellules est dissipée vers l'extérieur ;

les dimensions de la capsule étant suffisantes pour permettre l'implantation dans le corps du patient et la diffusion entre les cellules et le milieu environnant la capsule dans le corps.

33. Système selon la revendication 32, dans lequel la capsule comprend une pastille faite d'un copolymère acrylique de polyvinylchlorure.

34. Système selon la revendication 32, dans lequel la capsule comprend un tube à paroi mince.

35. Système selon la revendication 32, dans lequel les cellules vivantes sensibles au glucose sont sélectionnées à partir du groupe composé de cellules bêta, cellules sensorielles, cellules alpha, et de combinaisons entre elles.

36. Système selon la revendication 32, dans lequel la membrane présente une masse moléculaire critique ne dépassant pas environ 50 000.

37. Système selon la revendication 1, dans lequel ledit système comprend une capsule implantable dans le corps d'un patient, ladite capsule comprenant un tube à paroi mince ou une pastille et étant constituée de :

(a) cellules vivantes sensibles au glucose, capables de produire un signal électrique en réponse à la concentration de glucose dans le milieu environnant la capsule dans le patient ;
(b) une membrane cellulaire entourant chaque cellule, ladite membrane cellulaire contenant au moins un, et étant revêtue d'au moins un colorant dont les propriétés optiques sont modifiées par le signal électrique produit par lesdites cellules, et
(c) la seconde membrane étant imperméable aux cellules et à tous anticorps et grosses molécules pour empêcher des réactions immunologiques, et étant perméable aux substances nutritives des cellules, et aux déchets émanant des cellules, pour maintenir la viabilité des cellules ; les dimensions de la capsule étant suffisantes pour permettre l'implantation dans le corps du patient et la diffusion entre les cellules et le milieu environnant la capsule dans le corps.

38. Système selon la revendication 37, dans lequel la capsule comprend un tube à paroi mince.

39. Système selon la revendication 37, dans lequel la capsule comprend une pastille faite d'un copolymère acrylique de polyvinylchlorure.

40. Système selon la revendication 37, dans lequel les cellules vivantes sensibles au glucose sont sélectionnées à partir du groupe composé de cellules bêta, cellules sensorielles, cellules alpha, et de combinaisons entre elles.

41. Système selon la revendication 37, dans lequel la membrane présente une masse moléculaire critique ne dépassant pas environ 50 000.

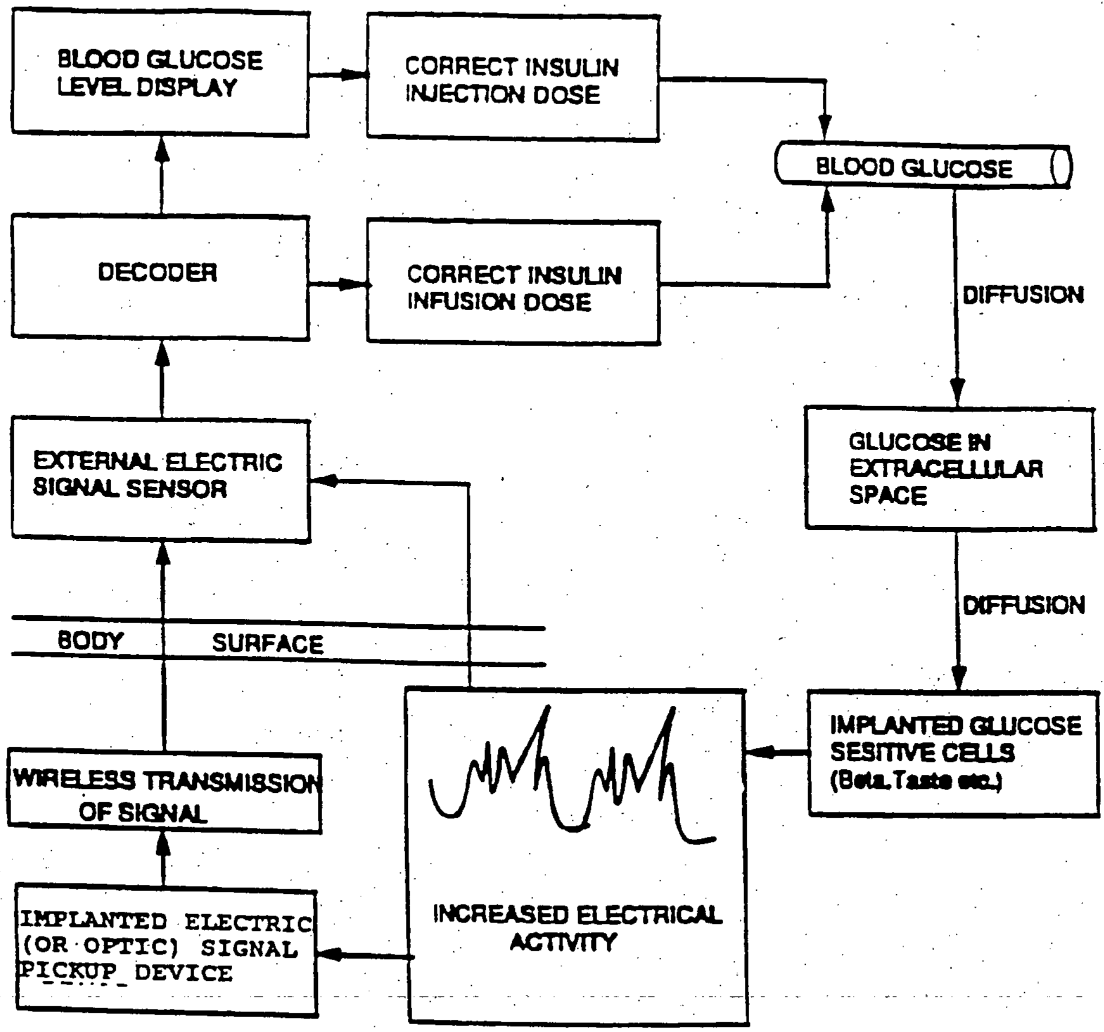

BLOOD GLUCOSE LEVEL DISPLAY
CORRECT INSULIN INJECTION DOSE
BLOOD GLUCOSE
DECODER
CORRECT INSULIN INFUSION DOSE
DIFFUSION
GLUCOSE IN EXTRACELLULAR SPACE
EXTERNAL ELECTRIC SIGNAL SENSOR
DIFFUSION
BODY SURFACE
IMPLANTED GLUCOSE SESITIVE CELLS (Beta,Taste etc.)
WIRELESS TRANSMISSION OF SIGNAL
INCREASED ELECTRICAL ACTIVITY
IMPLANTED ELECTRIC (OR OPTIC) SIGNAL PICKUP DEVICE

FIGURE 1

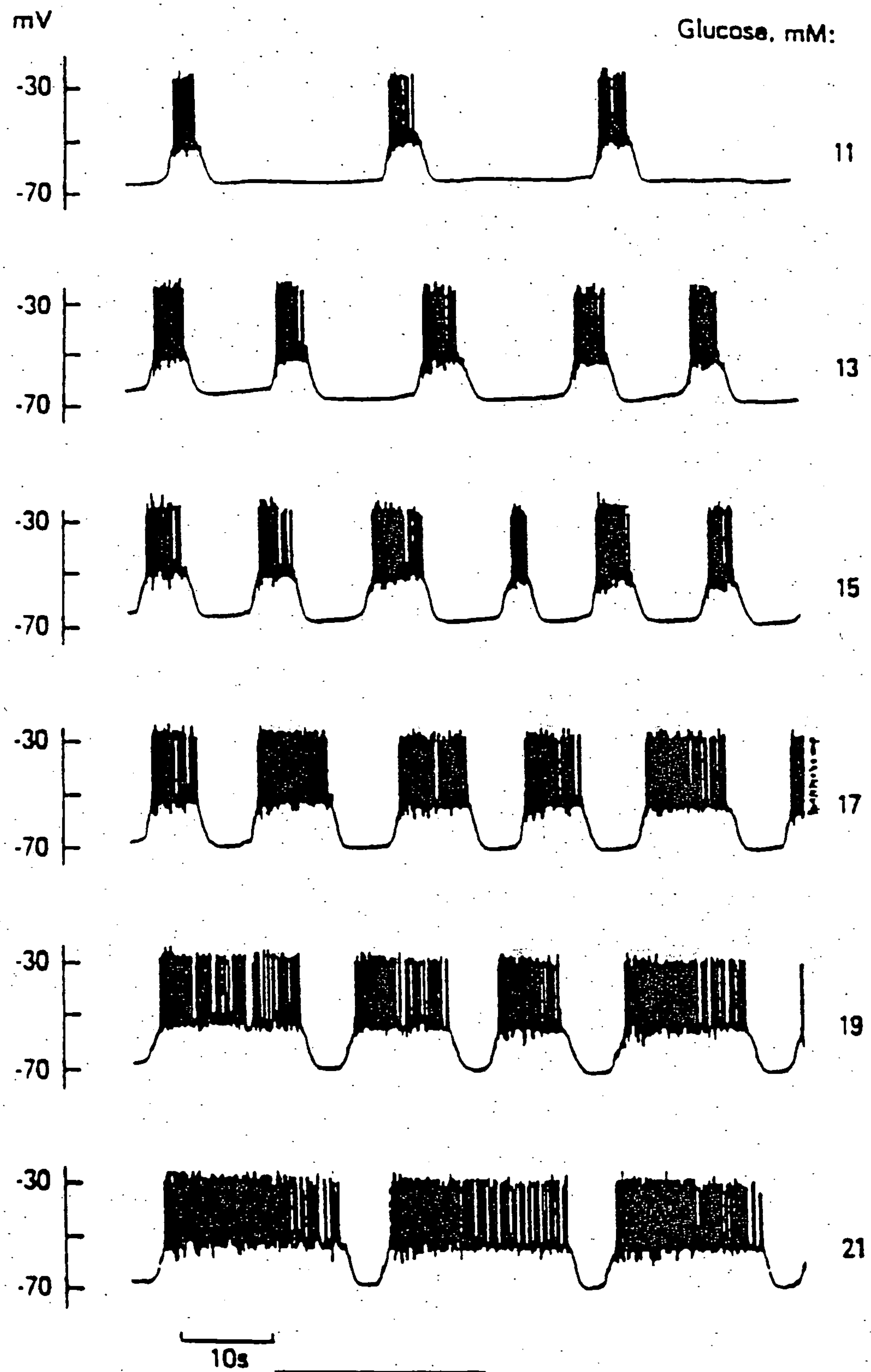
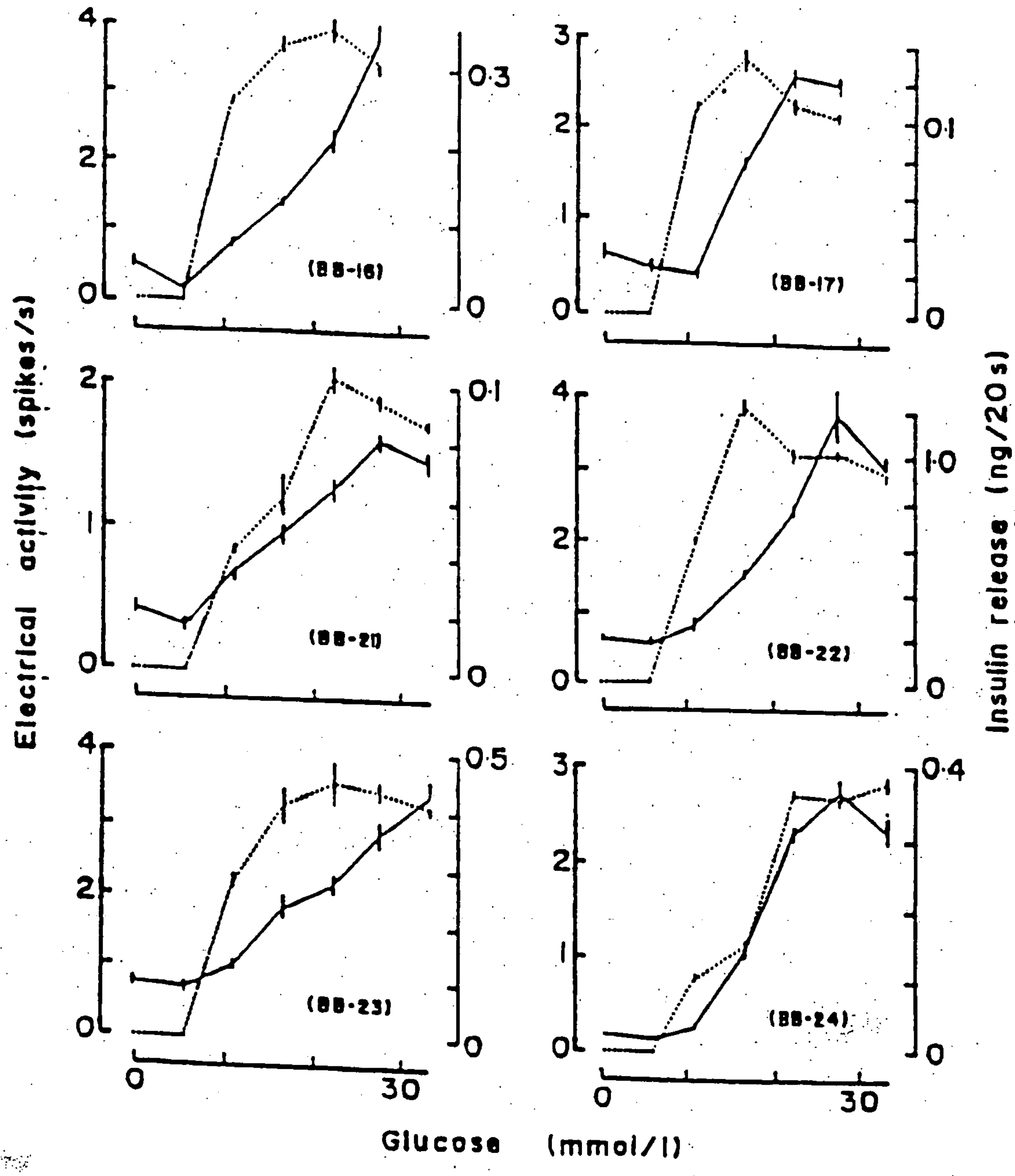

mV
Glucose, mM:
-30
-70
11
-30
-70
13
-30
-70
15
-30
-70
17
-30
-70
19
-30
-70
21
10s

FIGURE 2



Electrical activity (spikes/s)
Insulin release (ng/20 s)
(BB-16)
(BB-17)
(BB-21)
(BB-22)
(BB-23)
(BB-24)
Glucose (mmol/l)


FIGURE 3

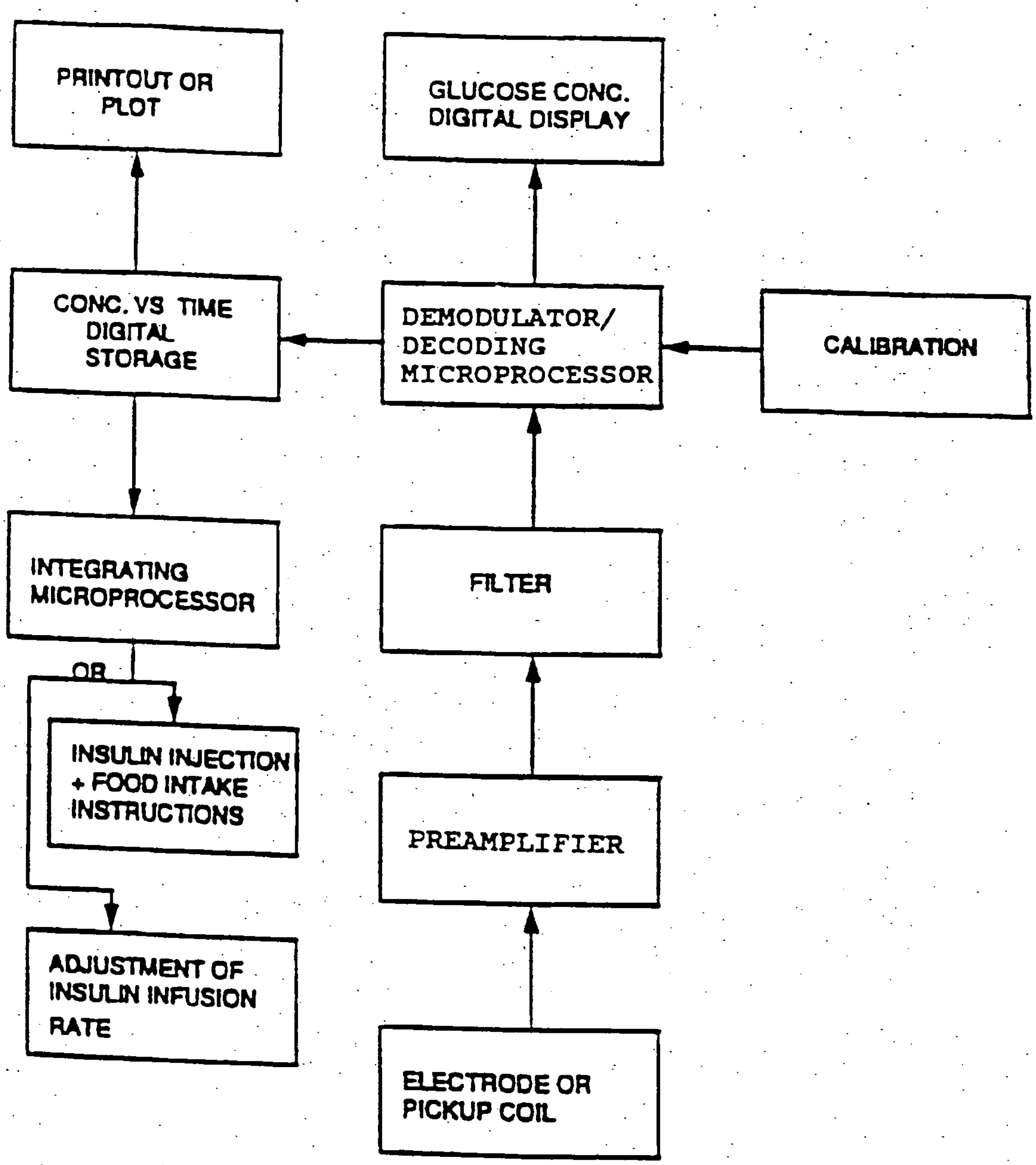

PRINTOUT OR PLOT
GLUCOSE CONC. DIGITAL DISPLAY
CONC. VS TIME DIGITAL STORAGE
DEMODULATOR/ DECODING MICROPROCESSOR
CALIBRATION
INTEGRATING MICROPROCESSOR
FILTER
OR
INSULIN INJECTION + FOOD INTAKE INSTRUCTIONS
PREAMPLIFIER
ADJUSTMENT OF INSULIN INFUSION RATE
ELECTRODE OR PICKUP COIL

FIGURE 4

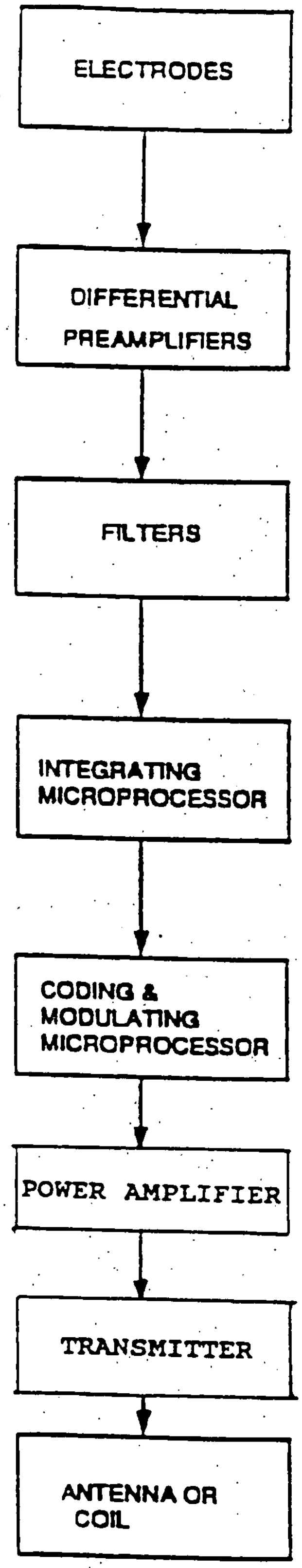

ELECTRODES
DIFFERENTIAL PREAMPLIFIERS
FILTERS
INTEGRATING MICROPROCESSOR
CODING & MODULATING MICROPROCESSOR
POWER AMPLIFIER
TRANSMITTER
ANTENNA OR COIL

FIGURE 5

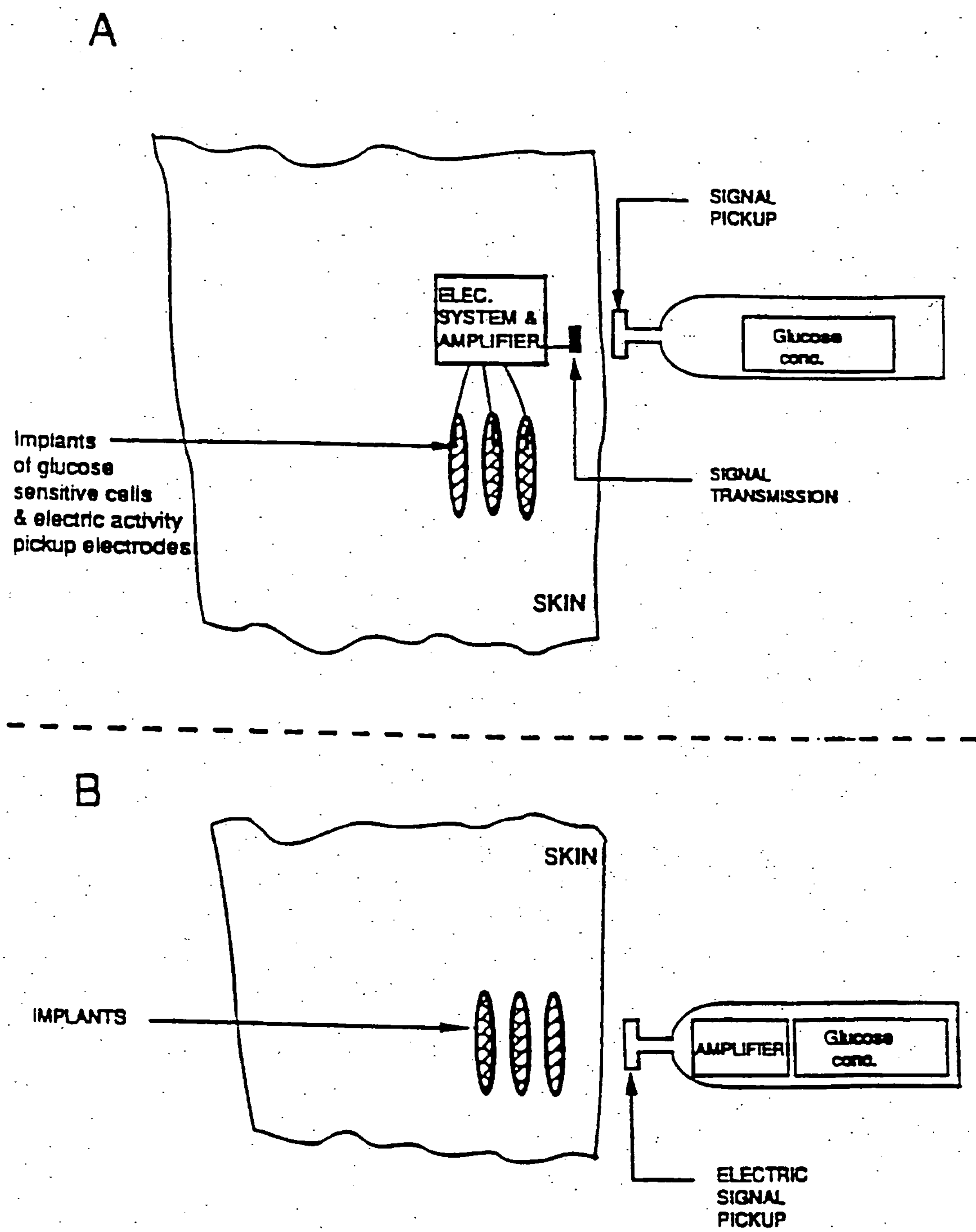

A
SIGNAL
PICKUP
ELEC.
SYSTEM &
AMPLIFIER
Glucose
conc.
Implants
of glucose
sensitive cells
& electric activity
pickup electrodes
SIGNAL
TRANSMISSION
SKIN
B
SKIN
IMPLANTS
AMPLIFIER
Glucose
conc.
ELECTRIC
SIGNAL
PICKUP

FIGURE 6

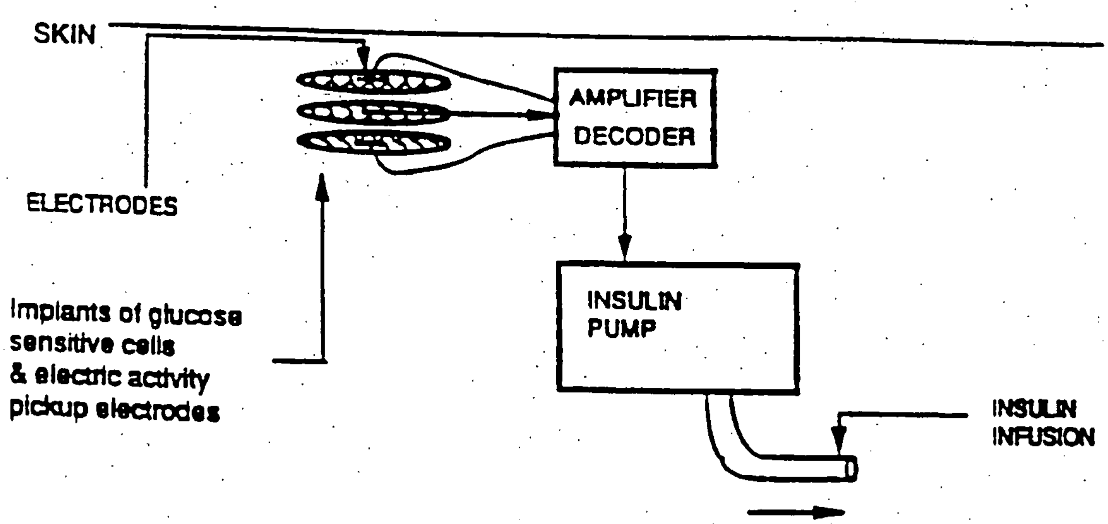

SKIN
ELECTRODES
AMPLIFIER
DECODER
INSULIN
PUMP
Implants of glucose
sensitive cells
& electric activity
pickup electrodes
INSULIN
INFUSION

FIGURE 7

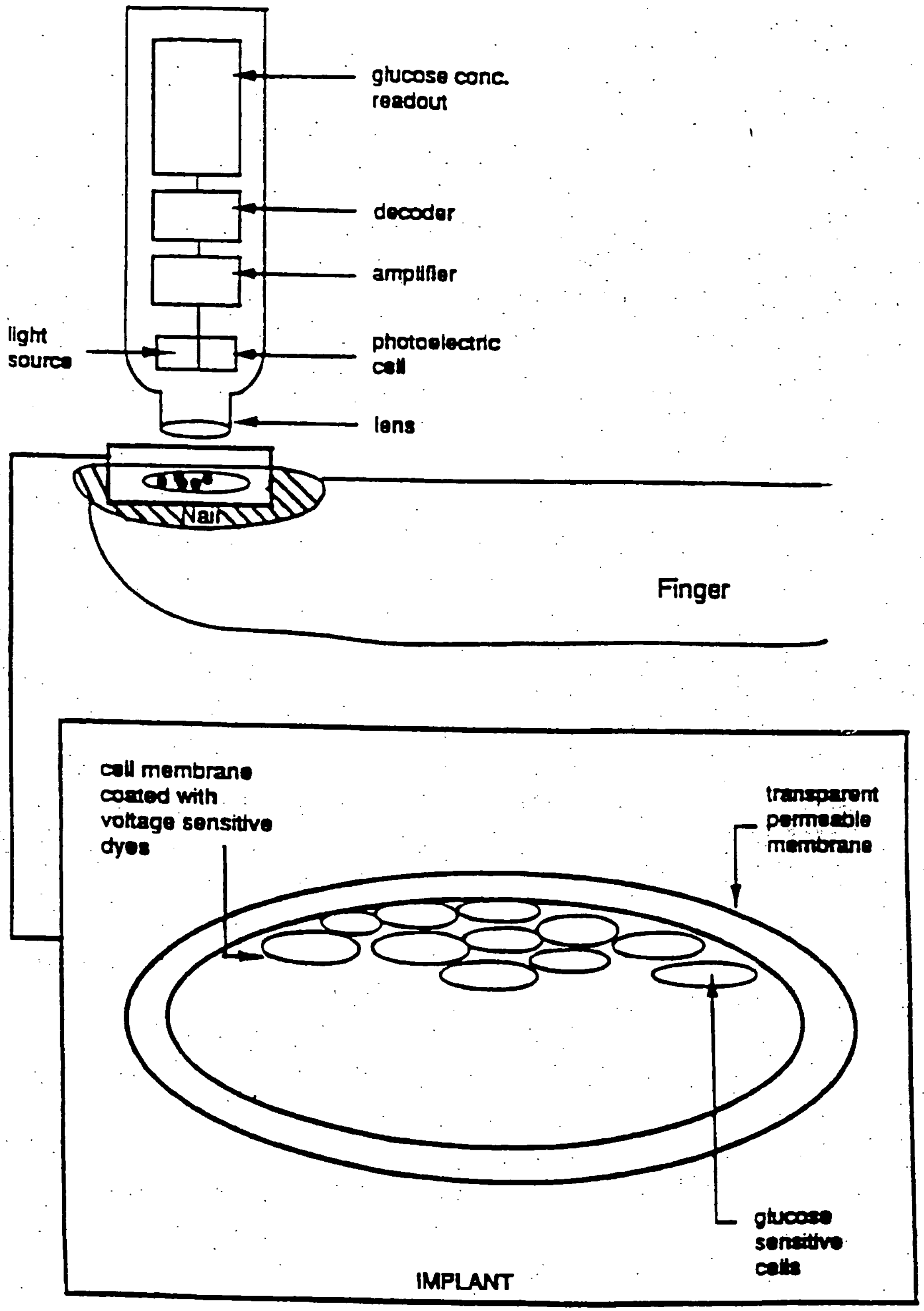

glucose conc. readout
decoder
amplifier
light source
photoelectric cell
lens
Nail
Finger
cell membrane coated with voltage sensitive dyes
transparent permeable membrane
glucose sensitive cells
IMPLANT

FIGURE 8